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Pustular Psoriasis and Associated Musculoskeletal Disorders

Kristina Callis Duffin[1], Hervé Bachelez[2], Philip J. Mease[3], Cheryl Rosen[4], Amit Garg[5], Eric Zudak[6], Ori Elkayam[7], Joseph F. Merola[8], Jeffrey Chau[9], Mitsumasa Kishimoto[10], Victoria Furer[7], and Philip S. Helliwell[11]

ABSTRACT. Pustular psoriasis (PsO) is an uncommon variant of PsO that may present in a generalized or localized fashion with or without musculoskeletal or systemic inflammatory involvement. Generalized pustular PsO (GPP) presents as a widespread acute or subacute pustular eruption that may be familial and is often associated with severe flares and systemic inflammation. The palmoplantar pustulosis variant is localized to palms and soles, whereas acrodermatitis continua of Hallopeau is localized to the nail apparatus. Patients with pustular PsO may have overlapping plaque PsO and may develop psoriatic arthritis (PsA). Pustulosis is also a feature of both synovitis, acne, pustulosis, hyperostosis, osteomyelitis (SAPHO) syndrome and chronic nonbacterial osteomyelitis. At the 2020 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting, members were given an overview of the cutaneous features of pustular PsO, SAPHO, and recent insights into the genetics of GPP, leading to new targeted drug therapies and the development of validated endpoints.

Key Indexing Terms: generalized pustular psoriasis, palmoplantar pustulosis, SAPHO

Pustular psoriasis (PsO) is an uncommon and challenging PsO phenotype with both generalized and localized presentations. The defining feature of pustular PsO is the presence of primary, sterile, and macroscopically visible pustules on the skin. In 2017, the European Rare and Severe PsO Expert Network (ERASPEN) published a historical overview and a consensus statement in which primary pustular PsO was classified into 3 types: generalized pustular PsO (GPP), palmoplantar pustulosis (PPP) and acrodermatitis continua of Hallopeau (ACH).[1]

Generalized Pustular PsO (GPP)

GPP, also known as GPP of von Zumbusch, is considered a rare, potentially life-threatening disorder characterized by acute and widespread flares of erythematous patches with pustules, with

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[1]K. Callis Duffin, MD, MS, Department of Dermatology, University of Utah, Salt Lake City, Utah, USA; [2]H. Bachelez, MD, PhD, Department of Dermatology, Hôpital Saint-Louis, AP-HP, and Laboratory of Genetic Skin Diseases, Imagine Institute, Université de Paris, Paris, France; [3]P.J. Mease, MD, Rheumatology Research, Swedish Medical Center/Providence St. Joseph Health and University of Washington School of Medicine, Seattle, Washington, USA; [4]C. Rosen, Division of Dermatology, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada; [5]A. Garg, MD, Chair, Department of Dermatology, Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA; [6]E. Zudak, BFA, Vice President, Strategic Partnerships, WCG Trifecta, Indianapolis, Indiana, USA; [7]O. Elkayam, MD, V. Furer, MD, Rheumatology Department, Tel Aviv Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [8]J.F. Merola, MD, MMSc, Harvard Medical School, Brigham and Women's Hospital, Department of Dermatology and Department of Medicine, Division of Rheumatology and Immunology, Boston, Massachusetts, USA; [9]J. Chau, GRAPPA Patient Research Partner, Hong Kong; [10]M. Kishimoto, MD, Department of Nephrology and Rheumatology, Kyorin University School of Medicine, Tokyo, Japan; [11]P.S. Helliwell, MD, PhD, Professor of Clinical Rheumatology, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Harehills Lane, Leeds, and NIHR Leeds Biomedical Research Centre, Leeds, UK.

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Address correspondence to Dr. K. Callis Duffin, University of Utah, 4A330 Dermatology, SOM, 30 North 1900 East, Salt Lake City, UT 84132, USA. Email: Kristina.callis@hsc.utah.edu.

or without systemic inflammation, and can be either relapsing or persistent. Acute generalized pustular PsO may present late in pregnancy and remit following delivery, historically called "impetigo herpetiformis," but this may not be clinically or histologically distinguishable from acute GPP and many consider it the same disorder. Approximately 30% of patients with GPP have concurrent plaque PsO. The prevalence of PsA in patients with GPP is unclear.

A groundbreaking advance in the understanding of GPP was the observation that it segregated in an autosomal recessive fashion in Tunisian consanguineous families, which led to discovery of a loss-of-function mutation in the *IL36RN* gene.[2] This gene encodes the interleukin (IL)-36 receptor antagonist, which prevents an uncontrolled inflammatory cascade, triggering PsO. This antagonist is very specific and does not cross-react with the IL-1 receptor. However, *IL36RN* mutations are only seen in 8–19% of patients.[3,4]

Palmoplantar Pustulosis (PPP) and Palmoplantar Pustular PsO (PPPP)

Palmoplantar pustulosis (PPP) is defined by presence of pustules on the palms and/or soles. Historically, there has been disagreement in including PPP in the spectrum of PsO, as it does not share the same genetic associations.[5] The ERASPEN classification distinguishes PPP from palmoplantar pustular PsO (PPPP) by the presence of concomitant plaque PsO. PPP tends to present later in life (mean age 48–69 yrs), and it is more common in women and in smokers.[6,7] The prevalence of PPP ranges from 0.01% in White populations to 0.12% in Japan, where it is associated with bacterial infections, including tonsillitis, sinusitis, or periodontal infections.[8,9] Tonsillectomy is reported to improve the symptoms of PPP. The Japanese literature also reports that around 30% develop musculoskeletal (MSK) disease, so patients with PPP are frequently followed by rheumatologists and orthopedists.

Acrodermatitis Continua of Hallopeau (ACH)

The third type of pustular PsO is acrodermatitis continua of Hallopeau (ACH). This variant is considered a form of pustular PsO localized to the nail apparatus. It has been described as the sole manifestation of pustulosis in some, but may progress to or overlap with plaque PsO, PPP, or GPP.[10] It is considered challenging to treat but numerous vignettes report successful use of several oral systemic and biologic drugs.

Treatments for GPP, PPP, and ACH

All types of pustular PsO have been seen in patients with primary plaque PsO, often when patients experience a trigger (e.g., infection, stress). Numerous medications, when initiated or when withdrawn, are known to precipitate a flare, including topical and systemic corticosteroids, tumor necrosis factor (TNF)-α agents, cyclosporine A (CSA), and some other biologics.

Treatments for GPP. Nearly all therapeutic recommendations for GPP, which include CSA, methotrexate (MTX), infliximab (IFX), secukinumab, ixekizumab, and brodalumab, are based on case series and open-label studies with relatively weak evidence supporting their efficacy. Both improvement and worsening have been reported with IFX and other TNF inhibitors. An open-label Japanese study of guselkumab showed that around 45% of patients with GPP achieved "very much improved" or "much improved" at Week 16 using the Clinical Global Impressions (CGI) scale.[11] However, GPP is associated with short-lived flares, which creates challenges in selecting the timing of endpoints to demonstrate efficacy vs simply capturing the usual course of flare and remission.

Given the advances in our understanding of the pathogenesis of pustular PsO, there is robust rationale for developing more tailored therapies, specifically by inhibiting the cascade by blocking the IL-36 receptor. Currently there are 2 different humanized antibodies, ANB019 (AnaptysBio) and spesolimab (BI-655130, Boehringer Ingelheim), being used in clinical trials for both GPP and PPP. The phase I study proof-of-concept for spesolimab demonstrated that following a single intravenous dose, 5 of 7 patients with GPP flares reached the GPP-specific physician global assessment (GPP-PGA) score of "clear" or "almost clear."[12] Of note, only 3 of 7 of the patients had *IL-36RN* mutations.

Treatments for PPP. High-quality evidence for PPP therapies is also limited. According to a recent Cochrane review, there are only 37 randomized clinical trials for PPP with no particular mechanism of action considered very effective.[13] Cyclosporine was studied in 2 placebo-controlled randomized trials.[14] The response rate in 1 trial comparing 1 mg/kg CSA was 50% vs 19% in the placebo group. The second trial used a higher dose (2.5 mg/kg) of CSA and found a 90% response rate compared with 21% in the placebo group. Acitretin, MTX, and other small molecules are all reported in small trials and case series.[13] There are numerous case reports and series showing biologics can be effective for PPP. However, a trial of etanercept demonstrated no advantage over placebo, and ustekinumab was less effective than placebo.[13] IL-17 and IL-23 inhibitors may be more efficacious. A placebo-controlled randomized phase III study of secukinumab for PPP showed that 26.6% of patients met the primary endpoint of 75% PPP Area and Severity Index (PPPASI) improvement at 16 weeks vs 14.1% in the placebo group.[15] A phase II trial of guselkumab for PPP in Japanese patients demonstrated 60% of patients receiving guselkumab met 50% improvement in the PPPASI vs 21% in the placebo. Of note, patients received 200 mg of guselkumab at Day 1 and Week 4 (twice that of its approved dose in most countries). This information harmonizes with studies that showed upregulation of p19, p40, and IL17A in PPP lesional skin, but this does not necessarily mean they are playing a central pathogenic role.[16] There are many ongoing clinical trials in PPP for anakinra, risankizumab, the IL-36 receptor antagonist drugs ANB019 and spesolimab, apremilast, granulocyte colony-stimulating factor inhibitors, and others.

Outcome Measures for GPP and PPP

One of the major barriers to developing therapies for pustular PsO is the lack of validated endpoints. Outcome measures, both physician- and patient-reported, are important in the assessment of the severity and response to therapy in clinical trials and in

clinical practice. Although many outcome measures are available for plaque PsO and PsA, the spectrum of phenotypes for pustular disease and associated MSK syndromes may warrant both the use of psoriatic disease measures and the development of new outcome measures. For example, in both GPP and PPP, induration is not a prominent feature, whereas pustulation and desquamation (present at the end of a flare) are key primary symptoms. However, both may overlap with plaque PsO, creating challenges in assessing the severity and responsiveness to change where patches of erythema and pustules may overlap with plaques.

Measurements of Severity

Pharmaceutical drug development in GPP and PPP has driven recent interest in the development and/or adaption of instruments to measure severity of disease. Studies of biologics for GPP in Japan (where GPP is more common) have utilized measures unique to GPP, such as the Modified Japanese Dermatological Association Severity Index (mJDA-SI), and plaque measures. The mJDA-SI is a composite measure that has commonly been used as a primary endpoint.[17] It quantifies body surface area involvement in 3 ways (area of erythema with pustules, total area with erythema, and area with edema, each scored 0–3), and markers of systemic disease (fever, white blood count, C-reactive protein, and serum albumin, each scored 0–2), which are then added to create a total score and severity assignment (1–6 = mild, 7–10 = moderate, and 11–17 = severe). This score is then used to apply the CGI scale, which is a dynamic scale taking into account changes in the mJDA-SI score and improvements in individual mJDA-SI components. Its complexity and dynamic nature are problematic for regulatory agencies, prompting the development and adaptation of other instruments, including the PsO Area and Severity Index (PASI), the Investigator's Global Assessment scale (IGA), or PGA. The GPP-PGA is a static, 5-point, 0–4 scale where severity is rated as clear (normal skin) to severe (severe erythema, high density of pustules or lakes of pus, with severe scaling and crusting).[12] PASI and modified versions of PASI, where induration is substituted with pustulation, have also been used.

Similar to GPP, PPP studies have largely used global assessments and PASI adaptations. Both the PPP-IGA and an adapted PASI (PPPASI) are modified so that degrees of induration are substituted with degrees of pustulation. PPP studies also utilize fresh pus appearance (white or yellow) and total pustule counts. Weaknesses of these measures include the lack of inclusion of secondary features, such as fissures or erosions, which greatly affect patients. Similar to GPP, there are no published studies where psychometric properties of these instruments have been assessed.

During the panel discussions held during the GRAPPA annual meeting session, the limitations of our understanding of pustular PsO and the lack of endpoint measures were discussed. The continual editing of the descriptive language and the ways in which measures are applied are problematic (e.g., scoring individual components like erythema, and averaging scores or not). The need to collaborate online during the pandemic has actually benefited efforts where sponsors are partnering with GPP and PPP opinion leaders to conduct online consensus scoring exercises for endpoints in development. Ideally, experts will partner in consensus exercises to develop core domain sets for GPP, PPP, and synovitis, acne, pustulosis, hyperostosis, osteomyelitis (SAPHO) syndrome, with the goal of determining what should be measured in all clinical trials for these disorders.

SAPHO Syndrome

SAPHO syndrome is a rare inflammatory MSK and cutaneous disorder initially named from presenting features from early case reports (synovitis, acne, pustulosis, hyperostosis, and osteomyelitis). This syndrome is not seen commonly in rheumatology practice, but large cohorts have been followed in France, Japan, China, and Israel.[18,19] The original French case series was notable for a high proportion of North African patients; although the subsequent genetic association of *IL36RN* with generalized pustular PsO was seen in Tunisian families, joint disease was not prevalent in those patients.[20] In Japan, the same constellation of findings was termed "pustulotic arthro-osteitis," where a significant association with tonsillitis, sinusitis, and odontogenic infection was observed.[9,21,22] SAPHO syndrome has overlapping features with chronic nonbacterial osteomyelitis (CNO), previously known as chronic recurrent multifocal osteomyelitis (CRMO), which is primarily seen in children, but can extend into adulthood. CNO is characterized by recurrent painful sites of osteitis, which are lymphocytic infiltrates in bones throughout the skeleton, often treated first with nonsteroidal antiinflammatory drugs (NSAIDs), and then with TNF inhibitors.[23] Because of the close overlap between SAPHO syndrome and CNO, the international research groups for both entities are coordinating an Outcome Measures in Rheumatology Clinical Trials core domain set project (Dr. Philip Mease, personal communication).

SAPHO syndrome has a spectrum of MSK features that can be progressive and overlapping.[24] Most adult cases have anterior chest wall involvement. Synovitis is usually a less common but severe part of the syndrome, typically presenting as peripheral oligoarthritis. Osteitis presents with pain and sometimes swelling of involved bone; medial clavicular, anterior chest wall, sacroiliac joint, and spinal involvement are most commonly reported. Hyperostosis, caused by endosteal or periosteal proliferation, is usually a later finding. Axial spondyloarthritis, enthesitis, diffuse idiopathic skeletal hyperostosis, and other inflammatory findings have been reported.[25]

Cutaneous features of SAPHO syndrome include acneiform and neutrophilic eruptions. Nodulocystic acne, which tends to be moderate to severe, and scarring, as well as related follicular inflammatory disorders like hidradenitis suppurativa, are reported. Pustulosis most commonly presents as PPP, but a variety of neutrophilic dermatoses are reported. Of note, a study examining radiologic nuclear scans observed that plaque PsO was commonly seen in patients with osteitis in this series.[26]

Treatment of SAPHO syndrome typically includes NSAIDs and local steroids as a first line of therapy. The next line of treatment may include bisphosphonates or conventional disease-modifying antiinflammatory drugs, such as MTX or colchicine. Biologics are not considered first-line, but when utilized, TNF-α

inhibitors are most commonly selected first. IL-23 and IL-17 inhibitors may also represent another therapeutic option.[27]

In a recently published survey of GRAPPA membership, the Japan Spondyloarthritis Society and Israeli Society of Rheumatology shed further light on the controversies around the classification and therapy of this disorder.[28] Respondents felt that PPP was the most prevalent cutaneous manifestation, and anterior chest wall the most common osteoarticular manifestation. While magnetic resonance imaging is considered the preferred imaging modality, bone biopsy was not recommended by most. This study highlighted that there is an unmet need for a consensus exercise addressing diagnostic criteria, treatment approaches, and validated physician and patient-reported endpoint measures to monitor severity and response. A GRAPPA working group has been formed to initiate an international collaboration to modify existing PsA screening tools, such as the PsO Epidemiology Screening tool to screen for the unique rheumatologic features of SAPHO syndrome (chest wall pain and radiologic findings).

Discussion

In summary, cutaneous pustular PsO, PsA in patients with GPP and PPP, and MSK syndromes like SAPHO syndrome present numerous diagnostic and therapeutic challenges. Inherited genetic abnormalities play a role in a subset of patients with GPP, and to a lesser degree, PPP. The discovery of the role of IL-36 in the regulation of innate immune skin and systemic responses has driven drug development for cutaneous pustular disease. Although pustulosis is a significant component in SAPHO, relatively little is known about its pathogenesis or the role of IL-36 in this syndrome. A recent survey has given insight into the current approach to treating SAPHO syndrome, demonstrating how the manifestations vary greatly across different populations. International collaborations to develop registries, collect biomarkers, and to conduct consensus exercises on disease classification and outcome measure development are needed.

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